Exploring the Comorbidity Mechanisms Between Asthma and Idiopathic Pulmonary Fibrosis and the Pharmacological Mechanisms of Bu-Shen-Yi-Qi Decoction Therapy via Network Pharmacology

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Research Article

Keywords: Asthma, IPF, BSYQ decoction, Network pharmacology, Molecule docking

Posted Date: October 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-898301/v1

Abstract

Backgrounds. Asthma and idiopathic pulmonary fibrosis (IPF) are common chronic diseases of the respiratory system in clinical practice. However, the relationship and molecular links between them remain unclear, and the current treatment's efficacy is disappointing. Bu-Shen-Yi-Qi (BSYQ) decoction has clinically proved to be effective in treating various chronic airway inflammatory diseases, including asthma and IPF. But the underlying pharmacological mechanisms are still to be elucidated.

Methods. This study searched the proteins related to asthma and IPF via TTD, CTD, and DisGeNET database. We then submitted them to the STRING database to establish the protein-protein interaction (PPI) network. The co-bioinformatics analysis was conducted by Metascape. The active ingredients of BSYQ decoction were screened from TCMSP、ETCM、BATMAN-TCM database and HPLC/MS experiment. Then we predicted the corresponding targets based on TCMSP、ETCM, and BATMAN-TCM database. The common targets for asthma and IPF treatment were recognized, and further GO and KEGG analyses were conducted with the DAVID platform. Finally, molecule docking via Autodock Vina was employed to predict the potential binding mode between core potential compounds and targets.

Results. One thousand three hundred thirty-three asthma-related targets and 404 IPF-related proteins were retrieved, 120 were overlapped between them, and much of the asthma-related proteins fall into the same statistically significant GO terms with IPF. One hundred sixteen active ingredients of BSYQ decoction were acquired, and 1535 corresponding targets were retrieved. Eighty-three potential compounds and 56 potential targets were recognized for both asthma and IPF treatment. GO and KEGG analysis indicated that the inflammation response, cytokine production, leukocyte differentiation, oxygen level response, etc., were the common pathological processes in asthma and IPF, which were regulated by BSYQ decoction. Molecule docking further predicted the potential binding modes between the core potential compounds and targets.

Conclusion. The current study successfully clarified the complex molecule links between asthma and IPF and found the potential common targets between them. Then we demonstrated the efficacy of BSYQ decoction for asthma and IPF treatment from the angle of network pharmacology, which may provide valuable references for further studies and clinical use.

Introduction

Asthma is one of the most common chronic non-communicable diseases, affecting about 334 million people worldwide and causing approximately 250,000 deaths[1]. It is a chronic inflammatory disease of the airway related to various cells (e.g., eosinophils, mast cells, T/B lymphocytes, airway smooth muscle cells, airway epithelial cells.) and cellular components. It is characterized by airway hyperresponsiveness and reversible airflow restriction, with recurrent wheezing, shortness of breath, chest tightness, and cough. Idiopathic pulmonary fibrosis (IPF) is one of the most aggressive forms of idiopathic interstitial pneumonia (IIPs), with a median survival time of 2–3 years after diagnosis and no efficient treatment.

The prevalence of IPF has been reported to range from 10 to 60 cases per 100,000 in the United States. It was 494 cases per 100,000 in 2011 among adults over the age of 65 years (twice as high as the prevalence recorded ten years earlier), the rates of hospital admissions and deaths due to IPF are also increasing[2]. It is characterized by varying degrees of inflammation and fibrosis of the lung parenchyma with no definite cause[3]. Both asthma and IPF are common chronic diseases of the respiratory system in clinical practice. However, the causal relationship and molecular link between asthma and IPF remain unclear.

Age and air pollution exposure are the common risk factors for asthma and IPF[4, 5]. Chronic airway inflammation, repeated lung tissue injury and repair, and eventually, pulmonary dysfunction are the foremost common pathological processes in asthma and IPF[6]. Macrophages and neutrophils play essential roles in the chronic inflammation and airway remodeling process by phagocytosis, degranulation, extracellular trap formation, exosome secretion, the release of cytokines and chemokines, and autophagy [6, 7]. In addition, asthma and IPF are severe multifactorial lung diseases with the common feature of lung remodeling in morphologically distinct compartments, notably the large or small airways and parenchyma. Abnormal deposition of extracellular matrix (ECM) proteins is a critical factor in the development of tissue remodeling that results in symptoms and impaired lung function [8]. Although there are several common risk factors and pathological processes between asthma and IPF, the treatment and prognosis are different. The anti-inflammatory and bronchodilator treatments for asthma are the mainstay used in a stepwise approach (SABA, LABA, ICS)[9]. However, glucocorticoid has poor curative effects for refractory and severe asthma. In addition, long-term use of glucocorticoids has serious side effects, including osteoporosis, hypertension, and peptic ulcer bleeding[10]. β2 receptor agonists can make airway airflow unobstructed and relieve dyspnea, but long-term use may lead to tachycardia, arrhythmia, tremor, headache.[11]. For IPF treatment, the anti-inflammatory therapy did not improve the outcome, and an immunosuppressive therapeutic strategy incorporating prednisolone and azathioprine was shown to increase mortality in the treatment of IPF[12, 13]. Only nintedanib and pirfenidone are practical and are approved worldwide for IPF treatment, which has transformed patient management[14, 15],but the effect is limited and has inevitable side effects such as gastrointestinal (dyspepsia and anorexia) and dermatological (photosensitivity)[16]. Respiratory physicians search for potential novel drugs from the traditional Chinese medicine (TCM) library to treat asthma and IPF.

TCM has progressively gained wider attention worldwide due to its specific theory and long historical clinical practice[17]. Unlike modern medicine, in TCM theory, syndrome differentiation and treatment are the essential diagnosis and treatment principles for disease. TCM syndrome is a specific set of symptoms or a pattern of symptoms presenting the body's internal and external condition at a particular stage[18]. Lung-kidney deficiency is the core common clinical syndrome type in clinical practice for asthma and IPF patients. Based on our real-world evidence study and tonify the kidney and replenishing qi is the most basic treatment principle[19, 20]. Bu-Shen-Yi-Qi formulae (BSYQ), consists of three herbs, including *Epimrdii Herba* (Yinyanghuo), *Radix Astragali* (Huangqi), and *Radix Rehmanniae* (Shengdihuang), has been demonstrated to be effective in the treatment of chronic airway inflammatory diseases based on our randomized, double-blind placebo-controlled parallel-group multicentre clinical

trials[21, 22]. Experiment studies demonstrated that BSYQ decoction could relieve airway inflammation, airway hyperresponsiveness, and airway remodeling in the OVA-induced asthma mice model[23–25]. It can also reduce collagen deposition in lung tissue of bleomycin-induced pulmonary fibrosis mice model and improve pulmonary fibrosis (our unpublished data). However, it is still challenging to clarify the mechanisms of the BSYQ formula in the treatment of asthma and IPF via routine methods because TCM formulae is a complex system with multiple components, multiple targets, and synergistic interactions among its components [26].

Based on polypharmacology and systems biology, network pharmacology integrates various biological data information such as genomics, proteomics, metabolomics, and bioinformatics. It expounds on the occurrence and development of diseases from the perspective of biological network balance, understanding the interaction between the body and drugs and guiding the rational design of drugs from the perspective of restoring or improving the balance of biological network, is considered to be the next-generation drug development paradigm[27–29]. At the same time, the guiding ideology of holistic view and balance view of TCM and the overall synergistic mechanism of TCM prescription compatibility coincide with the drug research and development model advocated by network pharmacology. Therefore, integrating the emerging network pharmacology and TCM theory will provide new opportunities and methods to discover bioactive components and biomarkers, reveal their action mechanism, and explore the modern scientific connotation of TCM prescriptions based on complex biological systems[30]. Some studies have elucidated the scientific basis and systematic features of herbal medicine to treat diseases via network pharmacology such as Xuefu Zhuyu decoction[31], Ma-huang decoction[32], Liu-Wei-Di-Huang pill[33], and Qingluoyin[34], etc.

In the present study, we first try to explore the potential molecule link between asthma and IPF and the possible therapeutic mechanisms of BSYQ formulae for asthma and IPF and then try to understand the modern scientific connotation of the TCM theory- same treatment for different diseases from the angle of network pharmacology (figure 1 depicts a flowchart of the entire research procedure).

Materials And Methods

1. Asthma & IPF related protein screening.

The known target proteins for asthma and IPF were screened from Therapeutic Target Database (TTD, http://bidd.nus.edu.sg/group/cjttd/), which is publicly accessible and provides comprehensive information about the known therapeutic protein, nucleic acid targets described in the literature, and the corresponding drugs/ligands directed at each of these targets, etc.[35]. Then we further searched the Comparative Toxicogenomics Database (CTD, http://ctdbase.org/)[36] and DisGeNET database[37] (https://www.disgenet.org/) to collect the proteins related to asthma and IPF. The public CTD is an innovative digital ecosystem that connects toxicological information for chemicals, genes, phenotypes, diseases, and exposures. It now provides 45 million toxicogenomic relationships for over 16 300 chemicals, 51 300 genes, 5500 phenotypes, 7200 diseases, and 163 000 exposure events [36]. DisGeNET

is a knowledge management platform integrating and standardizing data about disease-associated genes and variants from multiple sources. The latest release covers the full spectrum of human diseases (more than 24 000 diseases and traits, 17 000 genes, and 117 000 genomic variants)[37]. We searched the three databases with the keywords "asthma" or "idiopathic pulmonary fibrosis" and set the species to "Homo sapiens." Finally, we consolidated the information and removed duplicates. The common proteins of asthma and IPF were reserved for further analysis.

2. Bioactive ingredients collection and targets prediction

Potential active compounds of BSYQ decoction were screened from TCMSP(http://sm.nwsuaf.edu.cn/lsp/tcmsp.php)[38],BATMAN-TCM(http://bionet.ncpsb.org/batman-tcm)[39], ETCM (http://www.nrc.ac.cn:9090/ETCM/) database[40] and the data from our previous HPLC/MS study[41]. Then the candidate targets of the active compounds were predicted based on the three databases above. TCMSP consists of all the 499 Chinese herbs registered in the Chinese pharmacopeia with 29,384 ingredients, 3,311 targets, and 837 associated diseases, as well as the ADME-related properties such as oral bioavailability (OB), half-life (HL), drug-likeness (DL), and Lipinski's rule of five (MW, AlogP, TPSA, Hdon, Hacc), etc. [38] BATMAN-TCM is the first online bioinformatics analysis tool specially designed for the research of the molecular mechanism of TCM. [39] The ETCM database includes comprehensive and standardized information for the commonly used herbs and formulas of TCM and their ingredients. It can also provide predicted target genes of TCM ingredients, herbs, and formulas, according to the chemical fingerprint similarity between TCM ingredients and known drugs [40].

3. Protein-protein interaction (PPI) network construction and analysis.

We took the intersection of targets of BSYQ decoction and the common proteins between asthma and IPF,then further uploaded them to STRING[42] (https://string-db.org/) to generate the PPI network, the minimum required interaction score was set to high confidence (0.7) and limited to "Homo sapiens." The STRING database aims to collect, score and integrate all publicly available sources of protein-protein interaction information, and complement these with computational predictions and then achieve a comprehensive and objective global network, including direct (physical) as well as indirect (functional) interactions[42]. The final PPI network was established and visualized via Cytoscape 3.8.0[43]. The network parameters were calculated by NetworkAnalyzer. The MCODE app (based on vertex weighting) in Cytoscape 3.8.0 was used to search the highly connected sub-networks in the PPI network[44].

4. Gene Ontology (GO) and Pathway Enrichment Analysis.

To further explore the mechanisms of BSYQ for asthma and IPF treatment, the intersection of targets of BSYQ and the common proteins between asthma and IPF were additionally performed GO enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis via the online platform DAVID 6.8[45] (DAVID, https://david.ncifcrf.gov/) and Metascape [46] (https://metascape.org/).

5. Molecule docking

AutoDock vina was used in this study to evaluate the potential molecular binding mode between ingredients and candidate targets. The PyMol 2.3.0 (http://www.pymol.org/) and the online platform PLIP 2021[47](https://plip-tool.biotec.tu-dresden.de) were employed to analyze the docked structures. The crystal structures of the target proteins were downloaded from the RCSB Protein Data Bank (www.rcsb.org). Water and hetero molecules were removed, and hydrogen atoms were added by AutoDock tools (1.5.6). The 3D chemical structures of active ingredients were retrieved from the PubChem compound database (NCBI, USA) and subjected to minimize the energy via molecular mechanics-2 (MM2) force field in Chem 3D Pro. The protein-ligand docking active site center was defined by the location of the original ligand, and the dimensions of the grids were set at 30 × 30 × 30 Å in the x, y and Z directions, with a spacing of 0.375 Å between the grid points. The docked conformation corresponding to the lowest binding energy was selected as the most probable binding conformation.

Results

1. Asthma & IPF related proteins collecting and analyzing

One thousand three hundred thirty-three asthma-related targets and 404 IPF-related targets were retrieved from the TTD, CTD, and DisGeNET database (Duplicates were removed and detailed in additional table S1). Asthma and IPF disease-specific PPI networks were established (figure 2A, 2B). The top 15 core proteins based on two network topology parameters (degree and betweenness centrality) in asthma and IPF were displayed in Table 1 and Table 2. Then we found that VEGFA, TP53, EGFR, AKT1, EGF, IL6, STAT3, and MYC occupied the core positions in asthma and IPF specific PPI networks, indicating the essential roles of these proteins in the pathological process of asthma and IPF. Thus, these common core proteins were the potential targets for the treatment of asthma and IPF. To further exploring the molecule link between asthma and IPF, a co-bioinformatics analysis was conducted by Metascape. One hundred twenty proteins were overlapped in the two groups of protein lists (Figure. 2C). Much of the asthma-related proteins fall into the same statistically significant GO terms (such as response to oxygen levels, leukocyte differentiation, MAPK cascades, signaling by interleukins, response to growth factor and regulation of cytokine production, etc.) with IPF-specific proteins (Figure.2D), indicating the strong function association between the two comparison cohorts. The 120 common proteins were used for further analysis.

Table 1
Top 15 core proteins in the asthma-specific PPT network.

Protein Name	Degree	Betweenness Centrality	Protein Name	Degree	Betweenness Centrality
IL6	507	0.026602	TP53	463	0.038446
GAPDH	500	0.035006	INS	464	0.03671
AKT1	490	0.031011	GAPDH	500	0.035006
TNF	479	0.025118	AKT1	490	0.031011
INS	464	0.03671	IL6	507	0.026602
TP53	463	0.038446	TNF	479	0.025118
ALB	434	0.023965	ALB	434	0.023965
VEGFA	400	0.014278	EGFR	391	0.01915
EGFR	391	0.01915	HSP90AA1	243	0.019129
MAPK3	367	0.010079	MYC	360	0.014939
STAT3	362	0.010978	VEGFA	400	0.014278
MYC	360	0.014939	NME8	54	0.012606
CXCL8	358	0.008725	EGF	354	0.012404
EGF	354	0.012404	APP	236	0.012177
IL10	353	0.008187	MAPK1	316	0.012167

Table 2
Top 15 core proteins in the IPF specific PPT network.

Protein Name	Degree	Betweenness Centrality	Protein Name	Degree	Betweenness Centrality
IL6	129	0.049704	TP53	119	0.083659
AKT1	129	0.082012	AKT1	129	0.082012
TP53	119	0.083659	FN1	114	0.070219
EGFR	115	0.05726	EGFR	115	0.05726
FN1	114	0.070219	IL6	129	0.049704
VEGFA	112	0.046531	VEGFA	112	0.046531
EGF	110	0.029447	MYC	104	0.042975
TNF	108	0.020339	ESR1	88	0.039777
MYC	104	0.042975	EGF	110	0.029447
STAT3	100	0.026734	TERT	34	0.02814
JUN	98	0.027703	JUN	98	0.027703
IL1B	96	0.016969	ACTB	76	0.027551
CXCL8	96	0.016948	STAT3	100	0.026734
ESR1	88	0.039777	CDH1	87	0.026659
CDH1	87	0.026659	CFTR	28	0.025087

2. Active ingredients screening and corresponding targets prediction of BSYQ decoction.

After removing duplicates, 175 active ingredients were acquired and further submitted to TCMSP, BATMAN-TCM, and ETCM databases to get the corresponding targets. Finally, except for 59 components predicted no targets, 116 active compounds and 1535 related targets were retrieved (additional tables S2 and S3). The compound-target (C-T) network was constructed and analyzed via Cytoscape 3.8.0 (figure 3A, B). The C-T network consists of 1651 nodes (116 active compounds and 1535 potential targets) and 5255 edges. Two centrality indicators, degree and betweenness centrality, were calculated to identify the critical nodes within the network (figure 3B). Interestingly, both two types of centrality indicators uniformly confirmed the core 15 candidate compounds (including adenosine, cetylic acid, octadecanoic, linolenic acid and quercetin, etc.) and targets (including PTGS2, NCOA2, AR, ESR1, and PTGS1, etc.) of BSYQ decoction (Table 3 and Table 4).

Table 3
Top 15 active compounds in the C-T network according to degree and betweenness centrality.

Ingredient Name	Degree	Betweenness Centrality	Ingredient Name	Degree	Betweenness Centrality
Adenosine, Adenine Nucleoside	414	0.282464182	Adenosine, Adenine Nucleoside	414	0.282464
Cetylic Acid,Hexadecanoic Acid,Palmitic Acid	370	0.169742477	Linolenic Acid	259	0.175644
Octadecanoic? Acid,Stearic Acid	320	0.114930316	Cetylic Acid,Hexadecanoic Acid,Palmitic Acid	370	0.169742
Linolenic Acid	259	0.175644195	Quercetin	237	0.125366
Quercetin	237	0.125365848	Gamma-Aminobutyric Acid	224	0.121065
Gamma-Aminobutyric Acid	224	0.121065221	Octadecanoic? Acid,Stearic Acid	320	0.11493
Canavanine	149	0.069555043	FA	127	0.082434
Kaempferol	137	0.030226515	Canavanine	149	0.069555
luteolin	129	0.032355609	Sucrose	63	0.039162
FA	127	0.082434046	Uridine	82	0.037645
Beta-Sitosterol	115	0.02578383	D-Mannitol,Cordycepic Acid	98	0.034955
D-Mannitol,Cordycepic Acid	98	0.034955394	luteolin	129	0.032356
Lupeol	98	0.020896911	Kaempferol	137	0.030227
Isorhamnetin	89	0.011006298	Beta-Sitosterol	115	0.025784
sitosterol	83	0.010530446	3,5-Dimethoxystilbene	61	0.024598

Table 4
Top 15 candidate targets in the C-T network according to degree and betweenness centrality.

Protein Name	Degree	Betweenness Centrality	Protein Name	Degree	Betweenness Centrality
PTGS2	54	0.035328	PTGS1	42	0.035343
NCOA2	49	0.01164	PTGS2	54	0.035328
AR	48	0.020706	AR	48	0.020706
ESR1	46	0.004363	PPARG	23	0.015876
PTGS1	42	0.035343	ACHE	18	0.013354
RXRA	31	0.009231	NCOA2	49	0.01164
GABRA1	29	0.003085	TNF	12	0.0116
ESR2	28	0.001461	PPARA	12	0.01123
PIM1	27	0.004446	ADORA1	10	0.010569
HSP90A	27	0.001984	SCN5A	22	0.010239
PRSS1	26	9.40E-04	SHMT1	9	0.010117
PGR	25	4.98E-04	ATP1A2	18	0.009873
ATP1A1	24	0.005754	XDH	10	0.009636
AHR	24	0.004933	RXRA	31	0.009231
PPARG	23	0.015876	IL1B	8	0.009034

3. Potential ingredients and targets of BSYQ decoction for asthma and IPF therapy

To further explore the molecule mechanisms of BSYQ decoction for asthma and IPF therapy, we took the intersection of the target's profile of BSYQ decoction with the 120 common proteins between asthma and IPF. Finally, 56 potential targets were retrieved and were regarded as the potential targets for asthma and IPF treatment (figure 3C). Then a potential compound -potential target (PC-PT) network was established and analyzed (figure 3D). The PC-PT network consists of 139 nodes (83 potential compounds and 56 potential targets) and 371 edges. The core potential ingredients and targets based on the two network parameters were shown in Tables 5 and Table 6. Quercetin, luteolin, linolenic acid, adenosine, kaempferol, etc., were considered the potential core compounds, and PTGS2, ESR1, PTGS1, NOS2, and AKT1, etc. were the main potential targets of BSYQ for asthma and IPF therapy. We further constructed the PPI network with the 56 potential targets by STRING and searched the similar function clusters of the PPI network by MCODE analysis based on topology (figure 4). The top 15 core proteins based on the two topological parameters in the 56 potential targets PPI network were showed in Table 7. IL6, IL-1β, TNF, VEGFA, and AKT1, etc., played an essential role in the PPI network, indicating the crucial roles in treating asthma and IPF. Similar function subnetworks were constructed, function analysis showed that cluster 1

mainly participated in the interleukins signaling (figure 4B). Cluster 2 specifically regulates the reactive oxygen species (figure 4C). Cluster 3 mainly regulates the cytokines and inflammatory response (figure 4D). Then we performed the GO and KEGG analysis with the 56 potential targets (figure 5). KEGG pathway analysis showed that TNF signaling pathway, HIF-1 signaling pathway, cytokine-cytokine receptor interaction, toll-like receptor signaling pathway, and MAPK signaling pathway, etc. were enriched and regulated by BSYQ decoction (figure 5A, 5B), indicating the underline comprehensive mechanisms of BSYQ decoction for asthma and IPF treatment. We found that the 56 potential targets mainly participate in the regulation of the inflammatory response, nitric oxide biosynthetic process, and smooth muscle cell proliferation process, etc. (figure 5C)

Table 5
Top 15 potential compounds in the PC-PT network according to degree and betweenness centrality.

Ingredient Name	Degree	Betweenness Centrality	Ingredient Name	Degree	Betweenness Centrality
Quercetin	36	0.309833105	Quercetin	36	0.309833105
luteolin	20	0.074877417	Sucrose	6	0.104421054
Linolenic Acid	16	0.076791716	Adenosine,Adenine Nucleoside	15	0.079102825
Adenosine,Adenine Nucleoside	15	0.079102825	Linolenic Acid	16	0.076791716
Kaempferol	14	0.048065771	luteolin	20	0.074877417
Isorhamnetin	11	0.010756097	Kaempferol	14	0.048065771
Rhamnocitrin	10	0.00855788	Canavanine	6	0.033126673
Pratensein	10	0.00855788	FA	6	0.029886082
Formononetin	10	0.01317824	TGFBR2	4	0.029023858
Beta-Sitosterol	9	0.019445351	Fructose	4	0.019612123
Cetylic Acid,Hexadecanoic Acid,Palmitic Acid	8	0.017682546	Beta-Sitosterol	9	0.019445351
Kumatakenin	7	0.005434062	Cetylic Acid,Hexadecanoic Acid,Palmitic Acid	8	0.017682546
Canavanine	6	0.033126673	Hentriacontanol-6	2	0.014492754
Sucrose	6	0.104421054	Medicarpin	6	0.013850015
Octadecanoic? Acid,Stearic Acid	6	0.010597854	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	6	0.013850015

Table 6
Top 15 potential targets in the PC-PT network according to degree and betweenness centrality.

Protein Name	Degree	Betweenness Centrality	Protein Name	Degree	Betweenness Centrality
PTGS2	54	0.277312173	PTGS2	54	0.277312173
ESR1	46	0.153120648	PTGS1	42	0.204507204
PTGS1	42	0.204507204	ESR1	46	0.153120648
NOS2	19	0.032615148	CXCR4	8	0.086469588
AKT1	15	0.01512124	TNF	12	0.060803175
GSK3B	13	0.009859331	CYP3A4	12	0.058290209
CYP3A4	12	0.058290209	HMOX1	6	0.035902065
TNF	12	0.060803175	HIF1A	4	0.035245261
ACTB	10	0.013813159	ICAM1	5	0.034843635
MAPK14	10	0.001209612	NOS2	19	0.032615148
CEBPB	9	0.007230542	IL1B	8	0.031406599
ANXA1	8	0.014493758	TGFBR2	4	0.029023858
CXCR4	8	0.086469588	IFNG	4	0.016903104
IL1B	8	0.031406599	AKT1	15	0.01512124
IL6	6	0.009704189	SERPINE1	5	0.014896122

Table 7
Top 15 potential targets in the 56 potential targets PPI network

Protein Name	Degree	Betweenness Centrality	Protein Name	Degree	Betweenness Centrality
IL6	51	0.059767121	IL6	51	0.059767121
IL1B	46	0.034930701	EGFR	43	0.041706178
TNF	46	0.030700549	VEGFA	46	0.038701872
VEGFA	46	0.038701872	IL1B	46	0.034930701
AKT1	45	0.034171523	AKT1	45	0.034171523
PTGS2	44	0.027625229	TNF	46	0.030700549
EGFR	43	0.041706178	ESR1	33	0.030204633
EGF	42	0.022481519	PTGS2	44	0.027625229
JUN	40	0.025683985	JUN	40	0.025683985
CCL2	39	0.015488887	EGF	42	0.022481519
MMP2	37	0.009780132	MAPK14	34	0.021812819
IL4	36	0.013415867	CCL2	39	0.015488887
TGFB1	35	0.009526729	IL4	36	0.013415867
MAPK14	34	0.021812819	CEBPB	20	0.011576047
ICAM1	33	0.005648341	CXCL10	27	0.011252843

4. Molecule docking for the core potential ingredients and targets of BSYQ for asthma and IPF treatment

In the current study, the possible interaction modes between core ingredients and targets were predicted by Autodock vina. Molecule docking is a computational method that efficiently predicts the noncovalent binding of macromolecules or, more frequently, of a macromolecule (receptor) and a small molecule (ligand). It is generally believed that the lower the binding energy between ligand and receptor, the greater the possibility of interaction. Three core ingredients, including quercetin, luteolin, and kaempferol with four corresponding essential targets including AKT1, IL-6, PTGS2, and TNF, were docked and displayed to elucidate the exact binding mode (figure 6, A: kaempferol-AKT1; B: luteolin-AKT1; C: quercetin-AKT1; D: kaempferol-IL-6; E: luteolin-IL-6; F: quercetin-IL-6; G: kaempferol-PTGS2; H: luteolin-PTGS2; I: quercetin-PTGS2; J: kaempferol-TNF; K: luteolin-TNF; L: quercetin-TNF). Specifically, taking the kaempferol with AKT1, for example, five typical hydrogen bonds were established between kaempferol and AKT1 by engaging with essential amino acids such as SER205A, THR211A, and VAL271A inside the interfaced pocket created by active amino acid residues of AKT1. In the active site, there were also π-Stacking interactions between kaempferol and TRP80A, as well as hydrophobic interactions with TRP80A, LEU210A, and VAL270A, which helped stabilize the molecule at the binding site (figure 6A). Six key

hydrogen bonds with SER205A, THR211A, and VAL271A, hydrophobic interactions with TRP80A, LEU210A, LEU240A, and VAL270A, and π-Stacking interaction with TRP80A, were established between luteolin and AKT1 (figure 6B). Similarly, quercetin and AKT1 were shown to create five critical hydrogen bonds with SER205A, THR211A, and VAL271A, hydrophobic contacts with TRP80A, LEU210A, VAL270A, and ASP292A, and π-Stacking interaction with TRP80A (figure 6C). Between kaempferol and IL-6, seven important hydrogen bonds were discovered with ARG104A, GLU106A, SER108A, GLN156A, and ASP160A, as well as hydrophobic interactions with LYS46A and PHE105A, and π-Cation interactions with LYS46A were found (figure 6D). Five critical hydrogen bonds with THR43A, LYS46A, ARG 104A, GLU106A, and THR163A, hydrophobic interactions with LYS46A, ARG104A, and PHE105A, and π-Cation interactions with LYS46A and ARG 104A were formed between luteolin and IL-6 (figure 6E). Quercetin and IL-6 formed seven critical hydrogen bonds with GLU42A, ARG104A, GLU106A, SER107A, SER108A, and GLN156A, as well as hydrophobic interactions with LYS46A and PHE105A, and π-Cation interactions with LYS46A (figure 6F). Between kaempferol and PTGS2, six critical hydrogen bonds with ARG44A, ILE124A, ASP125A, SER126A, and GLN372A, as well as hydrophobic interactions with PRO542B and GLN543B, were discovered (figure 6G). Three key hydrogen bonds with SER126A and LYS546B, hydrophobic interactions with ARG44A, PRO542B, and GLN543B, were established between luteolin and PTGS2 (figure 6H). Quercetin and PTGS2 were shown to have three critical hydrogen bonds with ARG44A, SER126A, and LYS546B. Hydrophobic interactions with ARG44A, PRO542B, and GLN543B, and π-Cation interaction with ARG44A were predicted (figure 6I). Between kaempferol and TNF, four key hydrogen bonds with SER60B, GLN61A, TYR151A, and TYR151B, hydrophobic interactions with TYR59B and TYR119A, and π-Stacking interaction with TYR119A and TYR119B, were recognized (figure 6J). Five key hydrogen bonds with SER60B, LEU120B, GLY121A, TYR151A, and TYR151B, hydrophobic interactions with TYR59B and TYR119A, and π-Stacking interaction with TYR119A and TYR119B, were formed between luteolin and TNF (figure 6K). Quercetin and TNF established five critical hydrogen bonds with GLY121A, TYR151A, and TYR151B, hydrophobic interactions with TYR119A, and π-Stacking interactions with TYR119A (figure 6L). Taken together, hydrogen-bonding, π-stacking, π-cation, and hydrophobic interaction played key roles in the protein–ligand recognition and stability, which may be helpful for the activation or inhibition of the target proteins and is necessary for the pharmacology activities.

Discussion

Both asthma and IPF are inflammatory lung diseases characterized by airway injury, inflammation, bronchial and parenchymal remodeling[48]. The pathogenesis of asthma has not been fully defined, involving immunology, neuroendocrinology, genetic factors, and environmental factors. Airway hyperresponsiveness and airflow restriction are the main pathological features, and chronic inflammation is the main trigger. IPF is now generally considered the result of the interactions of multiple genetic and environmental risk factors. The aging alveolar epithelial repetitive local micro-injuries trigger abnormal epithelial fibroblast communication, induce myofibroblasts and a large amount of extracellular matrix accumulation, and pulmonary interstitial remodeling[49]. Chronic airway inflammation, epithelial-mesenchymal transformation (EMT), and oxidative stress also participate in the occurrence and

development of IPF[50, 51]. Thus, the repeated airway epithelial injury, chronic airway inflammation, EMT, airway remolding, and their interactions play essential roles in the pathological process both in asthma and IPF, indicating the similarity between the two different diseases. Unfortunately, the anti-inflammatory therapy for asthma can only control symptoms, and the improvement of disease progression is limited. It did not improve the outcome in the treatment of IPF, and an immunosuppressive therapeutic strategy incorporating prednisolone and azathioprine was shown to increase mortality [12, 13]. Corticosteroids and β-agonists are the cornerstones for asthma treatment. At the same time, they are nintedanib (targeting the tyrosine-kinases associated with platelet-driven growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor) and pirfenidone (inhibition of TGF-β signaling and reduction of fibroblast proliferation) for IPF. However, in the treatment of asthma, although corticosteroids can reduce inflammation and partially inhibit airway stenosis, they cannot reverse the progressive decline of lung function caused by airway reconstruction. In addition, long-term inhalation of corticosteroids still has a variety of adverse effects. The nintedanib and pirfenidone still cannot completely prevent the progressive decline of pulmonary function[52]. So, seeking new alternative therapies for IPF and asthma treatment is highly urgent and of far-reaching significance.

TCM is a comprehensive medicinal system that has been used in clinical practice for thousands of years and plays a vital role in the health maintenance of people all over the world[53, 54]. The validated curative effects of TCM make it a feasible alternative therapeutic agent for disease treatment[31]. Then, BSYQ decoction, proven effective, is regarded as the ideal joint therapy for asthma and IPF. In the current study, we first try to explore the complex molecule links between asthma and IPF, we constructed asthma and IPF specific PPI networks and compared the two protein profiles, the co-bioinformatic analysis showed that inflammation response, cytokine production, and leukocyte differentiation as well as oxygen level response, etc. commonly participate in the progress of asthma and IPF, and found there were 120 proteins overlapped. Additionally, eight proteins including VEGFA, TP53, EGFR, AKT1, EGF, IL6, STAT3, and MYC played essential roles in asthma and IPF. Then we searched the active compounds and predicted the corresponding targets based on the TCMSP, BATMAN-TCM, and ETCM databases. Finally, 175 active compounds (with 59 no predicted targets) and 1535 predicted targets were acquired. Then 83 potential targets anchored 56 common proteins between asthma and IPF, and the core potential compounds and targets were recognized. The additional GO and KEGG analysis indicated that inflammatory response, nitric oxide biosynthetic process, smooth muscle cell proliferation, etc., were mainly regulated by BSYQ decoction both in asthma and IPF. We also constructed the PPI network based on the STRING database, searched the similar function clusters, and further verified the potential binding mode between the potential compounds and targets via the molecule docking method. Unlike modern medicine anchored single targets, BSYQ decoction consists of 83 potential compounds and targets 56 common targets of asthma and IPF, regulated several pathways and biological processes, and showed a synthetic therapeutic effect.

IL-6, TNF, and AKT, which occupied an important position in asthma and IPF, are essential targets regulated by BSYQ decoction. IL-6 binds to sIL-6R and activates the membrane-bound glycoprotein 130 (gp130), then actives Jak/signal transducer and activator of transcription (STAT) signaling pathway[55],

which is implicated in a variety of inflammatory processes, including IPF[56, 57] and asthma[58]. Increased levels of tumor necrosis factor (TNF) α have been linked to several pulmonary inflammatory diseases, including asthma, chronic obstructive pulmonary disease (COPD), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), sarcoidosis, and IPF. TNF-α plays multiple roles in disease pathology by inducing an accumulation of inflammatory cells, stimulating the generation of inflammatory mediators, and causing oxidative and nitrosative stress, airway hyperresponsiveness, and tissue remodeling[48]. AKT regulates many processes, including metabolism, proliferation, cell survival, growth, and angiogenesis[59],and targeting the PI3K/AKT signal pathway is effective in treating asthma and IPF[59, 60]. In the present study, we found that IL-6 was anchored by 6 potential ingredients of BSYQ decoction (astragaloside Viii, magnograndiolide, soyasaponin 1, luteolin, quercetin, and aucuboside), TNF was targeted by 12 potential ingredients (adenosine, linolenic acid, sucrose, alexandrin, astragaloside Viii, magnograndiolide, soyasaponin 1, kaempferol, luteolin, quercetin, aucuboside, and cetylic acid) and AKT was hit by 11 ingredients (adenosine, DFV, formononetin, isorhamnetin, kaempferol, kumatakenin, luteolin, patensein, quercetin, quercitrin, and rhamnocitrin). Multi compounds anchored IL-6, TNF, and AKT and then produced synergistic effects. Representative flavonoids, including quercetin, kaempferol, and luteolin, were regarded as the core compounds for asthma and IPF treatment of BSYQ prescription based on our study. The anti-inflammatory and immunomodulating properties of quercetin are effectively utilized in the treatment of late-phase, and late-late-phase bronchial asthma responses, which is more competent in inhibiting IL-8 than cromolyn[61]. It can regulate the Th1/Th2 stability and decrease the antigen-specific IgE antibody releasing by B cells[62]. At the same time, it can reverse bleomycin-induced pulmonary fibrosis and attenuate lethality, weight loss, and the expression of pulmonary senescence markers by promoting FasL receptor and caveolin-1 expression and inhibiting AKT activation[63]. Kaempferol is a flavonoid found in many edible plants. Its anti-oxidant/anti-inflammatory effects have been demonstrated in disease models such as diabetes and asthma[64]. It can alleviate airway inflammation by modulating the Tyk2-STAT1/3 signaling response in the endotoxin-exposed airway epithelium in asthmatic mice[65]. But the efficacy of IPF treatment has not been evaluated. We found for the first time that it may be a potential agent for IPF therapy. Luteolin can modulated OVA-induced airway bronchoconstriction and bronchial hyperreactivity[66], inhibit autophagy by activating PI3K/Akt/mTOR signaling, and inhibiting Beclin-1-PI3KC3 complex[67]. It can reduce the weight index and hydroxyproline content, delay the process of pulmonary fibrosis and inhibit TGF-β1 mRNA expression in the bleomycin-induced pulmonary fibrosis model[68, 69]. In summary, multiple active ingredients in BSYQ decoction can act on various targets to treat diseases and then play a synthetic therapeutic effect.

Despite the profound significance of this study, several limitations should be noted. Firstly, the network construction and analysis separated from biological entities cannot fully reflect the internal network regulation mechanisms and dynamic changes of disease. Secondly, there is a dose-effect relationship between drugs and diseases, and the current network pharmacology method is challenging to achieve the purpose of quantification.

Conclusion

The relationship between asthma and IPF is complicated, and clinical and experimental studies have proved the efficacy of BSYQ decoction for treating asthma and IPF. In the current study, we successfully clarified the complex molecule links between asthma and IPF and found the potential common targets. Then we demonstrated the efficacy of BSYQ decoction for asthma and IPF treatment from the angle of network pharmacology, which may provide valuable references for further studies and clinical use.

Abbreviations

IPF
idiopathic pulmonary fibrosis
BSYQ decoction
Bu-Shen-Yi-Qi decoction
TTD
Therapeutic Target Database
CTD
Comparative Toxicogenomics Database
TCMSP
Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform
BATMAN-TCM
A Bioinformatics Analysis Tools for Molecular mechanism of Traditional Chinese Medicine
ETCM
The Encyclopedia of Traditional Chinese Medicine
TCM
Traditional Chinese Medicine
PPI
Protein-protein interaction
DAVID
The Database for Annotation, Visualization, and Integrated Discovery
AKT1
RAC-alpha serine/threonine-protein kinase
IL-6
Interleukin-6
PTGS2
Prostaglandin G/H synthase 2
TNF
Tumor necrosis factor
VEGFA
Vascular endothelial growth factor
TP53
Cellular tumor antigen p53

EGFR
Epidermal growth factor receptor
EGF
Pro-epidermal growth factor
STAT3
Signal transducer and activator of transcription 3
MYC
Myc proto-oncogene protein

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article (and its additional files)

Competing interests

The authors declare that they have no conflicts of interest.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Number: 81774074, 81973631), Shanghai Science and technology commission (Grant Number: 18401901800).

Authors' Contributions

Jingcheng Dong participated in the conception and design of the study. Yuanyuan Zhong, Lingli Hu, Wenjing Chen, and Bin Wang acquired and analyzed the data. Jing Sun drafted and revised the manuscript. The corresponding author and all the authors have read and approved the final submitted manuscript.

Acknowledgments

Not applicable.

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Figures

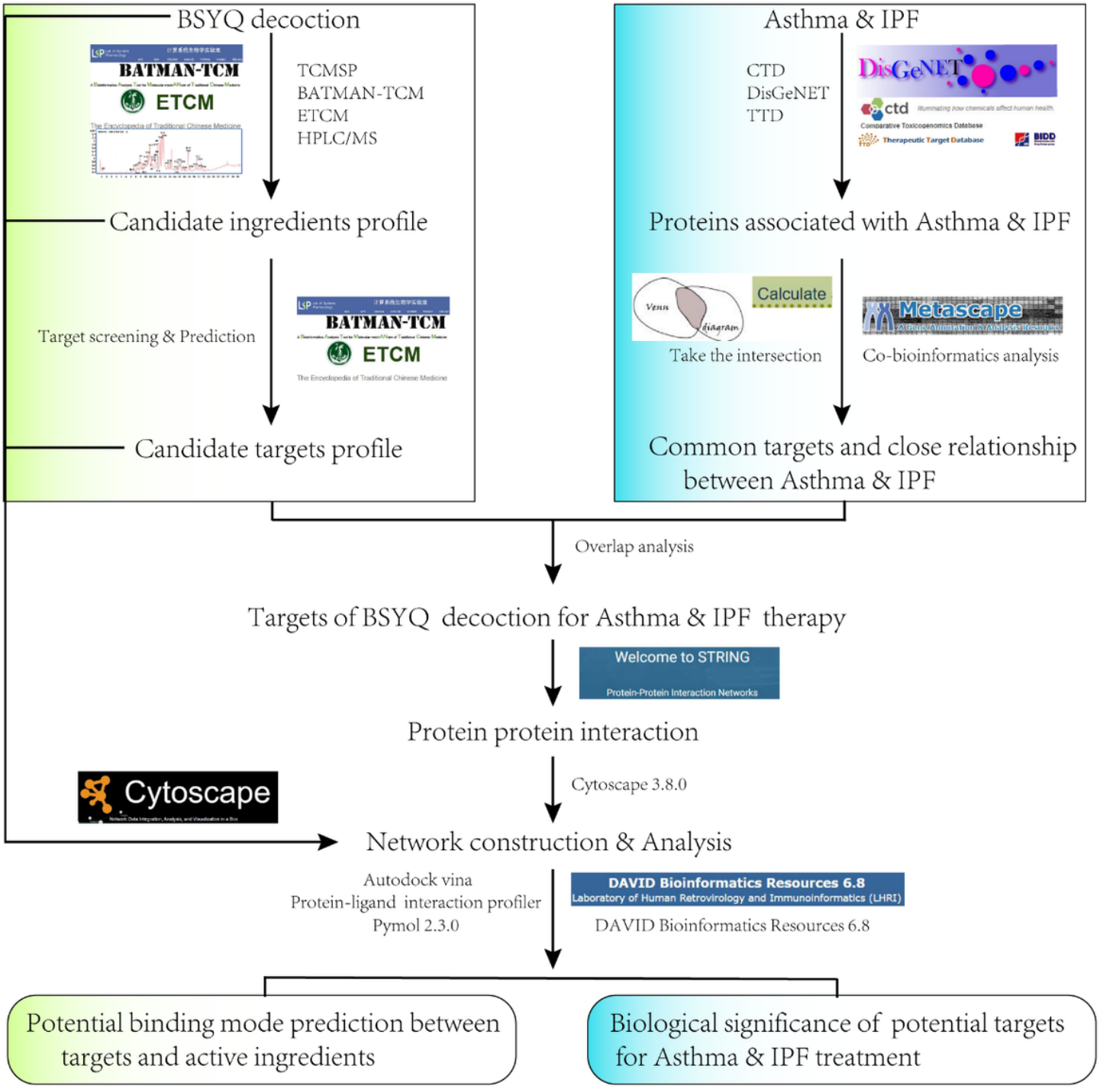


Figure 1

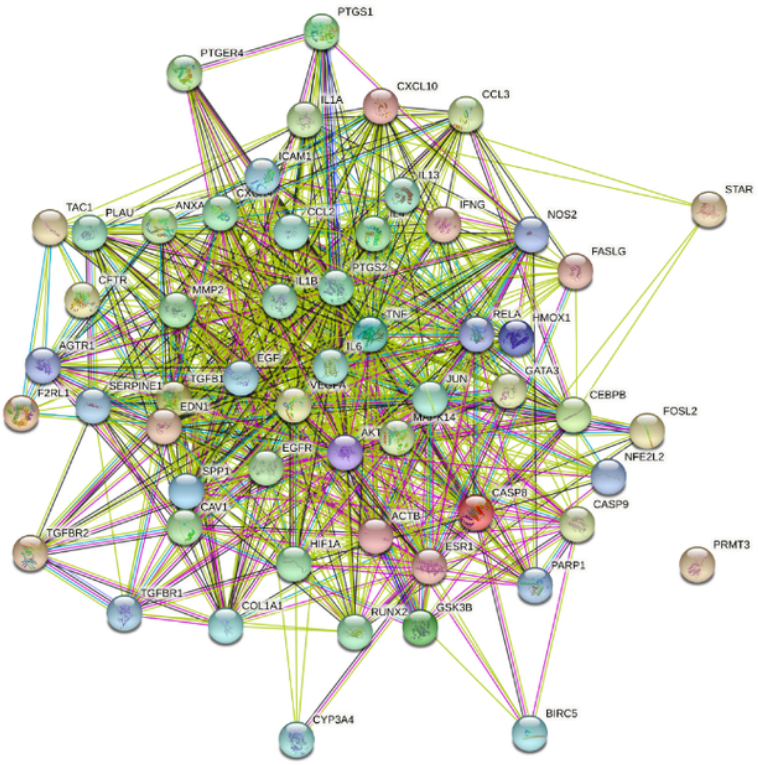
The flow chart of the current study.

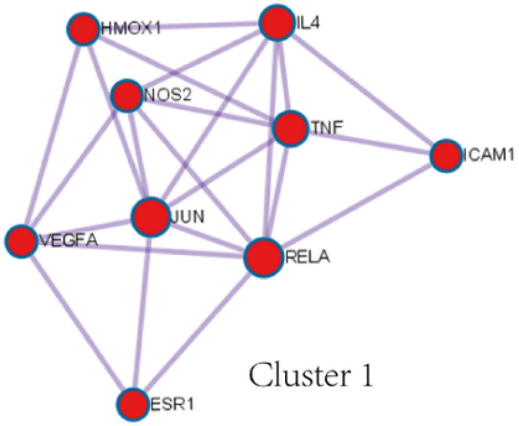
Figure 2

Asthma and IPF specific PPI network and co-bioinformatics analysis for the two protein profiles via Metascape. The size and color of the node are proportional to the value of degree and betweenness centrality (A and B). C: Circos plot for the two groups of proteins. Purple lines connect proteins that appear in both protein profiles. Blue lines connect proteins that belong to the same ontology term. D: Top 20 common GO terms or pathways enriched by the two protein profiles.

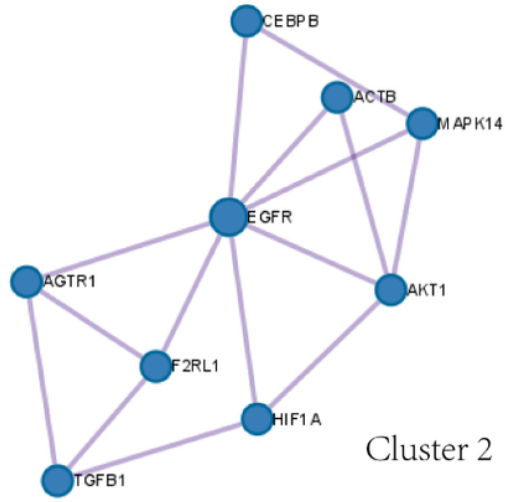
Figure 3

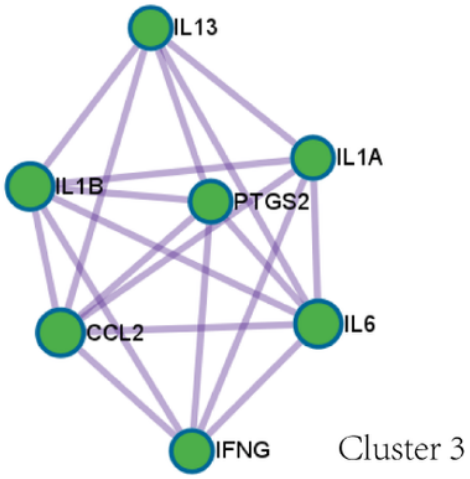
The analysis of the compounds and targets of BSYQ decoction and the potential targets screening for asthma and IPF treatment. A: The compound-target (C-T) network, B: the relationship between degree and betweenness centrality of the nodes in the C-T network, and the core compounds and targets of BSYQ decoction based on the two topology parameters were marked. C: the Venn diagram between targets of BSYQ and common proteins of asthma and IPF. D: The potential compound-potential target (PC-PT) network. The triangles and circles represent the compounds and targets, respectively.





Signaling by Interleukins (-13.4)
Interleukin-4 and Interleukin-13 signaling(-12.6)
IL-18 signaling pathway(-12.5)





IL-17 signaling pathway(-14.1)
Cytokines and inflammatory response(-14.0)

regulation of reactive oxygen species metabolic process (-14.3)
reactive oxygen species metabolic process(-13.0)
Proteoglycans in cancer(-11.0)

Figure 4

The protein-protein Interaction (PPI) network of the 56 potential targets for asthma and IPF therapy based on STRING. Similar function subnetworks were analyzed by Metascape.

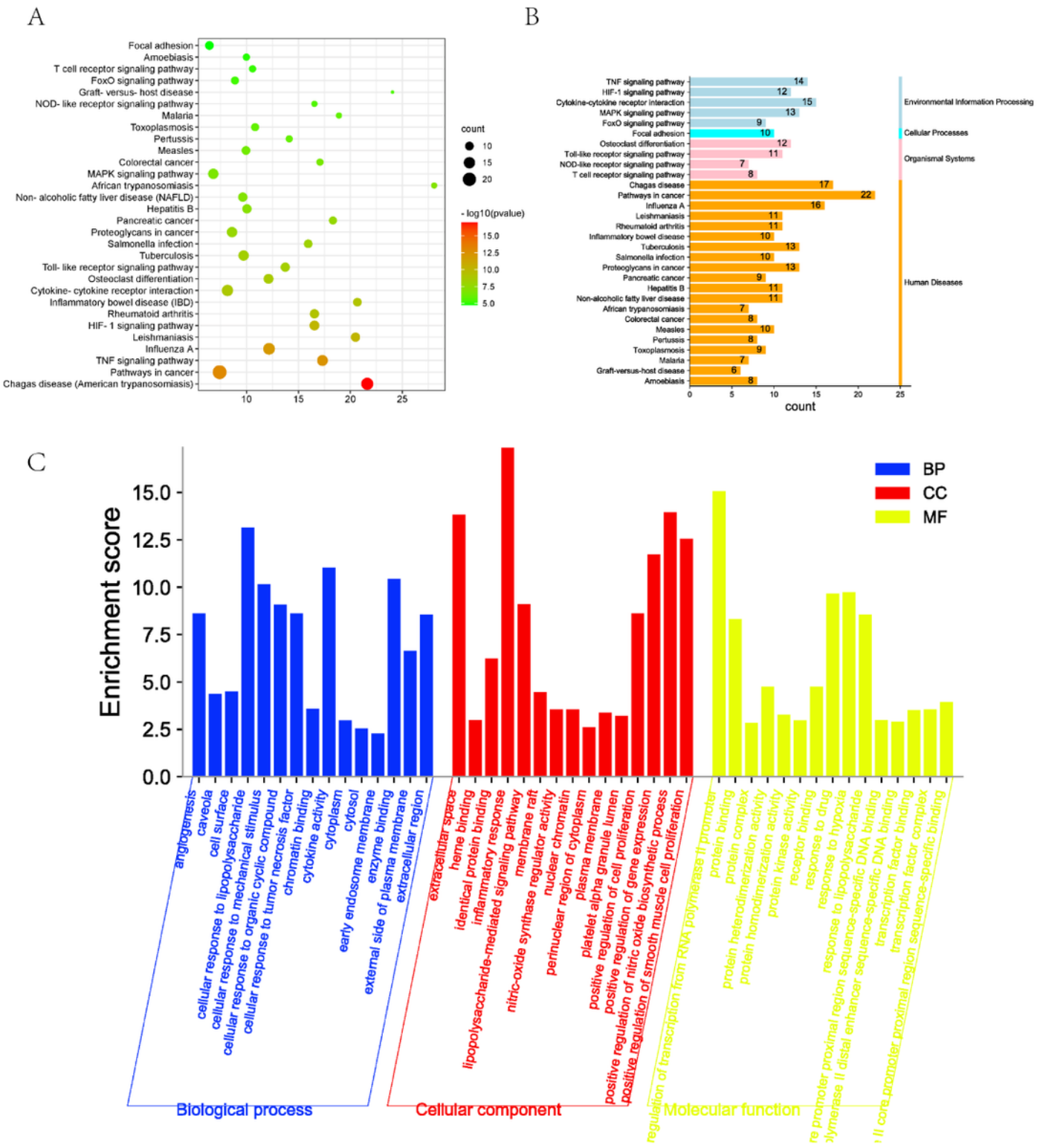


Figure 5

GO and KEGG analysis for the potential targets of BSYQ decoction for asthma and IPF therapy by DAVID 6.8. A and B: the top 30 enriched KEGG pathways of the 56 potential targets. C: the top 15 enriched GO items, including biology process (BP), cellular compartment (CC), and molecular function (MF).

Figure 6

Predicted binding mode within the active site of the drug-target complexes obtained from Autodock vina. A: kaempferol-AKT1; B: luteolin-AKT1; C: quercetin-AKT1; D: kaempferol-IL-6; E: luteolin-IL-6; F: quercetin-IL-6; G: kaempferol-PTGS2; H: luteolin-PTGS2; I: quercetin-PTGS2; J: kaempferol-TNF; K: luteolin-TNF; L: quercetin-TNF). The proteins were presented as cartoon modes, and molecules are presented as ball and stick models. Active site amino acid residues are represented as lines. Dotted blue lines in these pictures represent hydrogen bonds with distance units of ˚ A, dotted khaki lines represent π-Cation interactions, dotted red lines represent π-Stacking (parallel) interactions and dotted grey lines represent hydrophobic interaction. Other O and N atoms are colored red and blue, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionaltableS1.xlsx
- AdditionaltableS2.xlsx
- AdditionaltableS3.xlsx